Michael Condensations with Substituted Sorbic Esters. Part I. Methyl β-iso*Butenyl-αα'-dimethoxycarbonylglutarate.*

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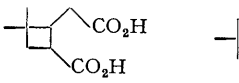
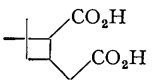
Dehydrobromination of 4-bromo-5-methylhex-2-enoic acid * and its methyl ester gave only low yields of the stereoisomeric δ-methylsorbic acids. Methyl δ-methylsorbate and methyl 5-methylhex-2-enoate failed to undergo Michael condensation with methyl malonate or methyl cyanoacetate. New syntheses of methyl α-cyano- and α-methoxycarbonyl-δ-methylsorbate are described. Michael condensation of the latter with malonic ester occurs by αβ-addition to at least 83% extent, giving methyl β-*iso*butenyl-αα'-dimethoxycarbonylglutarate. The glutaric ester adds hydrogen chloride to form a new chloro-ester, and with hydrogen bromide gives a bromo-ester that decomposes spontaneously by loss of methyl bromide to form a lactonic triester. Attempts to cyclise the chloro-ester with methyl sodio-*n*-propylmalonate yielded only products of dehydrochlorination and retro-Michael reactions. Acid hydrolysis of the Michael condensation product formed a new lactonic acid, and the latter with methanol formed the lactonic monoester and the corresponding unsaturated diester.

The experiments described in this paper were initiated several years ago with a view to develop an unambiguous synthesis of the second of the two isomeric formulations (I and II), and thus to reach a decision regarding the structure of caryophyllenic acid (Ruzicka and Zimmerman, *Helv. Chim. Acta*, 1935, **18**, 219; Ramage and Simonsen, *J.*, 1935, 532).

In an attempted synthesis of (II) from the dimethyl*bicyclo*heptenone (III) (Ramage and Simonsen, *Chem. and Ind.*, 1939, **58**, 447) difficulty was encountered in effecting complete reduction of the carbonyl group. However the later successful completion of this reduction by Dawson and Ramage (*J.*, 1950, 3523) indicated that caryophyllenic acid was (I), and this was confirmed by its direct synthesis by Campbell and Rydon (*Chem. and Ind.*, 1951, 312).

The present investigation sought an approach to structure (IV; R = H, CN, or CO_2Me; R' = CN or CO_2Me), since internal Michael condensation should lead to the *cyclo*butane derivative (V) (cf. Ingold, Perren, and Thorpe, *J.*, 1922, **121**, 1765), and the latter on hydrolysis and decarboxylation would furnish the acid (II).


(I)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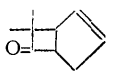
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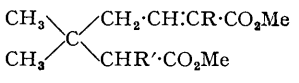
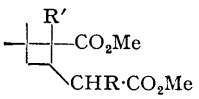

(IV)


(V)

$CHMe_2\cdot CH_2\cdot CH{:}CH\cdot CO_2R$
(VI)

$CMe_2{:}CH\cdot CH{:}CH\cdot CO_2R$
(VII)

5-Methylhex-2-enoic acid * (VI; R = H), best prepared by the Knoevenagel reaction of *iso*valeraldehyde with malonic acid in pyridine (von Auwers, *Annalen*, 1923, **432**, 50, 79), reacted readily with *N*-bromosuccinimide to give a bromo-acid that was dehydrobrominated only poorly by pyridine, and other bases, to furnish the stereoisomeric δ-methylsorbic acids (VII; R = H). Attempted Michael condensation of methyl malonate or cyanoacetate with methyl 5-methylhex-2-enoate (VI; R = Me) or δ-methylsorbate (VII; R = Me) failed. The sorbate was of special interest in view of Bloom and Ingold's speculation (*J.*, 1931, 2765) that δδ-dialkyl substitution in the diene system should favour formation of αβ-addition products at the expense of αδ-addition. It appeared entirely likely, however, that the inertia of the diene system in methyl δ-methylsorbate

* Geneva nomenclature, CO_2H = 1.

could be overcome by the suitable incorporation of additional electrophilic groups. Bloom and Ingold (*loc. cit.*) had indeed found that in the Michael condensation of cyanoacetic ester with sorbic ester and with crotonylidenemalonic ester, 10% of the total reaction occurred αβ-positions in the first case, and 16% in the second. Thus it seemed that methyl α-cyano- (VIII) or α-methoxycarbonyl-δ-methylsorbate (IX) might be suitable progenitors for the ultimate preparation of (IV), although it was realised that both δδ-dialkyl substitution and the αβ-situated electron sink should undoubtedly induce some αβ-addition and thus lessen the yield of the desired αδ-product.

The starting material for the synthesis of (VIII) and (IX) was β-methylcrotonaldehyde, best prepared by bromination of *iso*valeraldehyde and dehydrobromination (Fischer, Ertel, and Löwenberg, *Ber.*, 1931, **64**, 30; Fischer and Löwenberg, *Annalen*, 1932, **494**, 280). For the preparation of the sorbic esters, the acetal of β-methylcrotonaldehyde was hydrolysed with the theoretical quantity of water, acetic acid being used as catalyst as in the procedure of Cope *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 3452) for the preparation of alkylidenemalonic esters. Direct addition of piperidine and malonic or cyanoacetic ester to the hydrolysis mixture allowed the synthesis to be carried out without the usual loss occasioned by the isolation of the intermediate aldehyde.

Methyl α-cyano-β-methylsorbate (VIII) was isolated as a colourless crystalline substance, m. p. 74·5—75°. Andrews *et al.* (*ibid.*, 1945, **67**, 715) describe it as a yellow compound, m. p. 70·5—75°. The product, however, in typical Michael condensations gave inconclusive results in that only red acidic gums could be isolated from hydrolysis of the crude Michael products.

Methyl α-methoxycarbonyl-δ-methylsorbate (IX) was obtained as a colourless oil possessing a relatively high refractive index. The structure of this diene was clearly established by catalytic hydrogenation followed by hydrolysis and decarboxylation to 5-methylhexanoic acid, identical with that obtained by reduction and hydrolysis of methyl 5-methylhex-2-enoate (VI; R = Me).

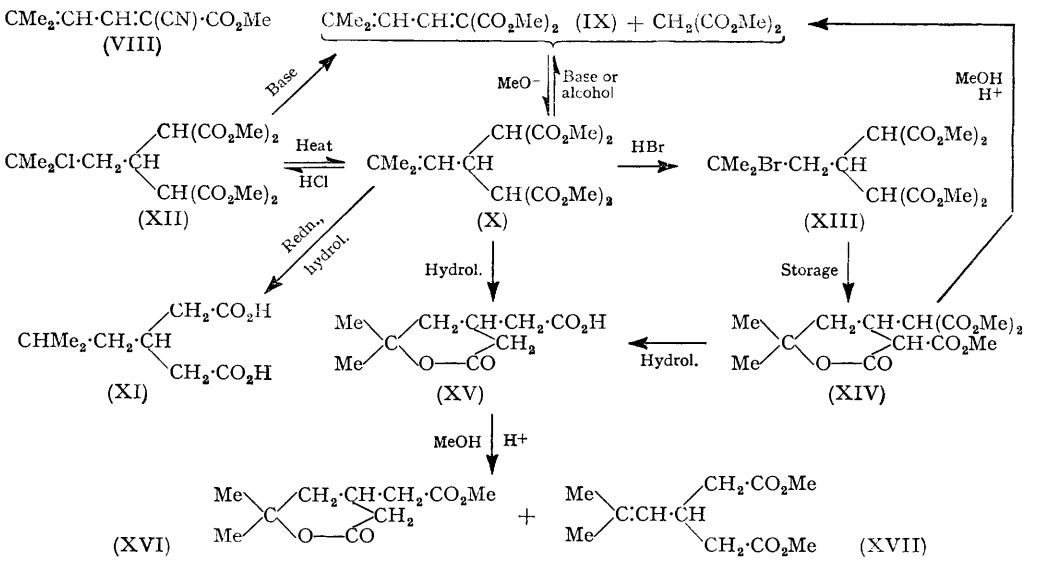
Under the conditions prescribed by Koelsch (*ibid.*, 1943, **65**, 437) the dicarboxy-ester (IX) reacted readily with methyl malonate and sodium methoxide to yield methyl β-*iso*but-2-enyl-αα′-dimethoxycarbonylglutarate (X) as a viscous almost colourless oil. The *exclusive* formation of this αβ-addition product (at least 83% yield) was surprising, and critically hindered our approach to the acid (II) although several attempts were made to transform this substance into the *cyclo*butane derivative (V). The reactions used to substantiate the structure of this Michael adduct, and the various transformations encountered in this work are set forth in the reaction scheme annexed.

The Michael product (X) proved to be exceedingly sensitive. It undergoes a complete retro-Michael reaction not only on contact with base, but also in the presence of alcohol. The latter reaction occurred during an unsuccessful attempt to reduce the compound in presence of Adams's catalyst and methanol. The products recovered were the sorbic ester (IX) and methyl malonate. For the successful reduction of the compound it was necessary to use massive amounts of Adams's catalyst in glacial acetic acid. Acid hydrolysis of the resulting dihydro-ester gave β-*iso*butylglutaric acid (XI), isolated as the anhydride in 87% overall yield from the glutaric ester (X). For comparison authentic anhydride was prepared (Curtis *et al.*, *J.*, 1923, **123**, 3131). Substantiation of αβ-addition was also secured by ozonolysis of (X), giving small yields of tricarballylic acid.

Acid hydrolysis of the Michael addition product furnished the crystalline lactonic acid (XV), whose structure is based upon analysis, titration, and the assumption of a normal Markovnikov addition of water to the ethylenic bond of the glutaric ester (X). Esterification of the lactonic acid with methanol–acid gave a 51% yield of the lactonic ester (XVI), together with a 28% yield of methyl β-*iso*butenylglutarate (XVII). It may be noted that the lower yield of the diester (XVII) implies formation of this compound from the lactonic ester by acid-catalysed dehydration of the intermediate tertiary alcohol.

With the structure of the Michael adduct established it seemed desirable to ascertain whether the Thorpe–Ingold effect (Ingold, *J.*, 1925, **127**, 387), so prominent in the α-halogeno-glutaric acid series, would be operative in promoting cyclisations involving internal alkylation of the malonic ester group in the glutarate (X). Boron trifluoride

was without effect on (X), and our attention then turned to attempted cyclisations of the hydrogen halide derivatives.



In carbon tetrachloride, (X) readily absorbed 1 mol. of hydrogen chloride to form the crystalline chloro-derivative (XII), which, in contradistinction to the ester of β-chloro-γ-methylvaleric acid (Bredt, *Ber.*, 1886, **19**, 513), was unstable to heat and could not be distilled *in vacuo* without quantitative loss of hydrogen chloride to regenerate the glutaric ester (X). Ring closure of the chloro-ester (XII) by internal alkylation was attempted by equilibrating the chloro-ester in xylene with ethyl sodio-*n*-propylmalonate. The choice of this reagent was based upon the facts that it was soluble in xylene, that it would be sterically unsuitable for intermolecular alkylation with the chloro-ester, and that it should form an anion of approximately the same basic strength as the anion derived from a malonic group within the chloro-ester itself. The latter, on displacement of the chloride ion might then be expected to undergo cyclisation. Actually the products of this reaction resulted from dehydrochlorination followed by a retro-Michael reaction, giving the sorbic ester (IX) together with methyl malonate and ethyl *n*-propylmalonate.

In view of the lower electrophilic nature of bromine, it appeared that use of the corresponding bromo-ester might be more profitable. However, although the Michael adduct readily reacted with hydrogen bromide in carbon tetrachloride, the bromo-ester (XIII) spontaneously lost methyl bromide on concentration of the solution, yielding the crystalline lactone (XIV), whose structure was readily proved by acid hydrolysis to the lactonic acid (XV). Attempts to regenerate the bromo-ester (XIII) by the action of methanolic hydrogen bromide gave only methyl malonate and methyl α-methoxycarbonyl-δ-methylsorbate (IX), resulting from a retro-Michael reaction of the glutarate (X), which must be assumed to be an intermediate in the last reaction. It may be noted that this behaviour of the lactonic ester (XIV) is different from that of the simple γ-methyl-γ-valerolactone (Bredt, *loc. cit.*) which on treatment with alcoholic hydrogen bromide readily yields its γ-bromo-ester, the latter regenerating the lactone only on distillation. The differences between the behaviour of the simple γ-methylvaleric models and our more involved *iso*-butenylglutaric esters are obviously due to the intense driving force of the retro-Michael reaction which furnishes the conjugated methyl α-methoxycarbonyl-δ-methylsorbate as the end-product.

Experimental

δ-Methylsorbic Acid (VII; R = H).—5-Methylhex-2-enoic acid (VI; R = H) (11·3 g., 0·0885 mole), prepared according to von Auwers (*loc. cit.*), in carbon tetrachloride (35 ml.) was

treated with *N*-bromosuccinimide (15·75 g., 0·0885 mole), reaction being started by warming (infra-red lamp). Succinimide was separated by filtration, and the filtrate was washed with water, dried, and distilled. The bromo-acid (14·2 g.) boiled at 115—124°/3 mm. It was dissolved in 18·5 ml. of pyridine and, after being kept overnight, refluxed for 15 min. The resultant crystalline mass was dissolved in ether and dilute sulphuric acid. The ethereal solution was freed from pyridine by washing it with dilute acid and was then extracted with sodium hydroxide solution. A chloroform extract of the acidified aqueous solution furnished a mixture of oil and solid on evaporation. Recrystallisation of the solid from hexane yielded *trans*-δ-methylsorbic acid (3·8 g.), m. p. 104·5—105° (Found : C, 66·5, 66·5; H, 8·0, 8·0. Calc. for $C_7H_{10}O_2$: C, 66·6; H, 8·0%).

Esterification of the acid in methanol and ethylene dichloride with sulphuric acid (Clinton and Laskowski, *J. Amer. Chem. Soc.*, 1948, **70**, 3135) gave *methyl δ-methylsorbate* (VII; R = Me), b. p. 79—79·5°/9·5 mm., $n_D^{21\cdot4}$ 1·5141 (Found : OMe, 22·3. $C_7H_9O{\cdot}OMe$ requires OMe, 22·1%).

Attempted Michael Reaction with Methyl δ-Methylsorbate.—A mixture of methyl δ-methylsorbate (3·94 g., 0·0281 mole) and methyl cyanoacetate (2·80 g., 0·0281 mole) in absolute methanol (10 ml.) containing 10 drops of piperidine became deep violet-red in 16 days. Only the starting materials and 0·5 g. of viscous, dark red oil were isolated on working up. Hydrolysis of the oil with 6N-hydrochloric acid gave a small amount of oil, not acidic to bicarbonate. Likewise, no evidence could be found of Michael reaction with methyl malonate. Methyl 5-methylhex-2-enoate (VI; R = Me) was also inert.

Methyl α-Cyano-δ-methylsorbate (VIII).—β-Methylcrotonaldehyde diethyl acetal (15·8 g., 0·1 mole) (Fischer, Ertel, and Löwenberg, *loc. cit.*) was hydrolysed with acetic acid (1·2 g., 0·02 mole) in water (1·8 g., 0·1 mole). After the addition of methyl cyanoacetate (9·9 g., 0·1 mole) and piperidine (0·17 g., 0·002 mole) the solution was set aside for 3 hr.; crystallisation was then induced by scratching. Methyl α-cyano-δ-methylsorbate was obtained as a colourless solid, m. p. 74·5—75° (Found : C, 65·2; H, 6·7; OMe, 18·7. Calc. for $C_8H_8ON{\cdot}OMe$: C, 65·4; H, 6·7; OMe, 18·8%).

To a solution of (VIII) (4 g., 0·024 mole) in methyl cyanoacetate (2·4 g., 0·024 mole) and a few ml. of methanol were added 4 drops of 2·17M-sodium methoxide. The solution became orange-red in 5 days. No evidence of a Michael addition product was obtained.

Methyl α-Methoxycarbonyl-δ-methylsorbate (IX).—β-Methylcrotonaldehyde diethyl acetal (15·8 g., 0·1 mole) was hydrolysed with glacial acetic acid (1·2 g., 0·02 mole) and water (1·8 g., 0·1 mole). After the addition of methyl malonate (13·2 g., 0·1 mole) the mixture was cooled in ice, and piperidine (0·34 g., 0·004 mole) was added. The solution was allowed to warm to room temperature and, after 36 hr., was diluted with ether and washed free from piperidine. The yield of *methyl α-methoxycarbonyl-δ-methylsorbate*, b. p. 107—110·5°/1·5 mm., n_D^{25} 1·5165, varied from 24 to 39% [Found : C, 58·8, 58·6; H, 7·2, 6·95; OMe, 31·1, 31·5. $C_8H_8O_2(OCH_3)_2$ requires C, 60·6; H, 7·1; OMe, 31·3%. 0·1825 G. of ester absorbed 0·00187 mole of hydrogen (Calc. : 0·00184 mole)].

Methyl β-iso*But*-1-*enyl-αα'-dimethoxycarbonylglutarate* (X).—Methyl malonate (13·6 g., 0·103 mole) was mixed with (IX) (20·37 g., 0·103 mole). After the addition of 9 drops of 3·26M-sodium methoxide, the mixture was set aside at room temperature for a few hours and then overnight at 5°. Ten drops of glacial acetic acid were added to the cold mixture, which was then taken up in ether, washed with dilute acid and water, dried, and evaporated. Fractionation of the residue yielded 25·94 g. (83%) of *methyl* β-iso*but*-1-*enyl-αα'-dimethoxycarbonylglutarate*, a pale yellow, viscous liquid, b. p. 122—132°/0·1 mm., $n_D^{25\cdot3}$ 1·4593 [Found : C, 54·6; H, 6·95; OMe, 37·2. $C_{11}H_{10}O_4(OCH_3)_4$ requires C, 54·5; H, 6·7; OMe, 37·6%].

Ozonolysis of (X) gave only a small yield of tricarballylic acid.

Hydrogenation of (X) could be achieved only by the use of Adams's catalyst in the proportion of 1·5 g. of catalyst to 4 g. of compound in 20 ml. of glacial acetic acid. Hydrolysis of the reduced ester and distillation of the product gave β-*iso*butylglutaric anhydride (87·4%), b. p. 150—156°/0·8 mm., n_D^{25} 1·4555 (Found : C, 63·3; H, 8·5. Calc. for $C_9H_{14}O_3$: C, 63·5; H, 8·3%); the residue was a few drops of red oil.

The anilic acid prepared from the anhydride melted at 140—140·5°, undepressed on mixture with the anilic acid prepared from authentic β-*iso*butylglutaric anhydride.

β-(2-*Hydroxy*-2-*methylpropyl*)*glutaric Acid* δ-*Lactone* (XV).—The Michael product (X) (10·52 g., 0·032 mole) was refluxed overnight with 7N-hydrochloric acid (50 ml.) under nitrogen. Isolation of the acidic product yielded the *lactone*, m. p. 98·5—100° (corr.) (2·95 g.) (Found : C, 58·2; H, 7·4%; equiv., 93·6. $C_9H_{14}O_4$ requires C, 58·05; H, 7·6%; equiv., 93·1).

The lactonic acid (2·25 g., 0·01209 mole) was refluxed with methanol (2·94 ml., 0·0725 mole),

ethylene dichloride (7·26 ml.), and 2 drops of sulphuric acid, and the two esterification products were isolated in the usual manner, *viz.*: *methyl* β-*but*-1′-*enylglutarate* (XVII) (0·725 g., 28%), b. p. 101—113°/0·76 mm., n_D^{21} 1·4467 [Found: C, 61·2; H, 8·8; OMe, 29·1. $C_8H_{12}O_2(OMe)_2$ requires C, 61·7; H, 8·5; OMe, 29·0%]; and α-*methyl* β-(2-*hydroxy*-2-*methylpropyl*)*glutarate* δ-*lactone* (XVI) (1·235 g., 51%), b. p. 125·5—126°/0·3 mm., n_D^{21} 1·4622 (Found: C, 59·4; H, 7·8; OMe, 15·2. $C_9H_{13}O_3$·OMe requires C, 60·0; H, 8·05; OMe, 15·5%).

Methyl β-(2-*Chloro*-2-*methylpropyl*)-αα′-*dimethoxycarbonylglutarate* (XII).—Hydrogen chloride (2·5 g., 0·0686 mole) was dissolved in a solution of 16·35 g. of Michael product (X) (0·0495 mole) in dry carbon tetrachloride (50 ml.) at 0°. The solution was set aside for 24 hr. at 0° and for 36 hr. more at room temperature. On removal of the solvent at reduced pressure, the solid product crystallised slowly. Recrystallisation from benzene–hexane gave the *ester* (XII), m. p. 63—63·5° (Found: Cl, 9·6. $C_{15}H_{23}O_8Cl$ requires Cl, 9·7%). Vacuum-distillation yielded the Michael product (X).

Equilibration of the Chloro-ester (XII) *with Ethyl Sodiopropylmalonate.*—Sodium (1·4 g., 0·061 g.-atom) was dissolved in a solution of ethyl *n*-propylmalonate (12·3 g., 0·061 mole) in xylene (25 ml.). This solution (7·25 ml., containing 0·0095 mole of ethyl sodiopropylmalonate) was added in portions of 12—15 drops to a stirred solution of the chloro-ester (3·485 g., 0·0095 mole) in dry xylene (14 ml.) at 53—55°. Each addition was made only after the solution had returned to neutrality. Next morning a few drops of glacial acetic acid were added to the neutral solution. It was then diluted with xylene (50 ml.) and worked up. The products were ethyl *n*-propylmalonate, the Michael product (X), methyl malonate, and methyl α-methoxycarbonyl-δ-methylsorbate (IX).

Methyl β-(2-*Hydroxy*-2-*methylpropyl*)-αα′-*dimethoxycarbonylglutarate Lactone* (XIV).—Hydrogen bromide (1·7 g., 0·021 mole) was dissolved in an ice-cold solution of Michael product (X) (7·08 g., 0·0214 mole) in carbon tetrachloride (50 ml.). After 40 hr. at room temperature, the solution was freed from solvent at reduced pressure. After 4 days the residual bromo-ester (XIII) deposited a solid, which on recrystallisation from benzene–hexane proved to be the *lactone* (XIV), m. p. 76—77° (1·25 g., 18·5%) [Found: C, 53·2; H, 6·3; OMe, 29·0. $C_{11}H_{11}O_5(OMe)_3$ requires C, 53·2; H, 6·4; OMe, 29·4%].

Treatment of the lactone-ester with hydrogen bromide and methanol gave methyl malonate, methyl α-methoxycarbonyl-δ-methylsorbate (IX), and a small amount of starting material.

Attempted Cyclisation of the Michael Product (X) *with Boron Trifluoride.*—Boron trifluoride was dissolved in an ice-cold ethereal solution of the Michael product. The wine-red solution was stored at 0° for 3 days and worked up. Only unchanged starting material was recovered.

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